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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,752	11/27/2000	Manuel Baca	P1093PID1	6340

9157 7590 01/17/2003

GENENTECH, INC.  
1 DNA WAY  
SOUTH SAN FRANCISCO, CA 94080

EXAMINER
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HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 01/17/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/723,752

Applicant(s)

BACA ET AL.

Examiner

Larry R. Helms

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 04 November 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 43-47 and 49-59 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 43-47, 49, 50 and 53-59 is/are rejected.
- 7) ☒ Claim(s) 51 and 52 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: notice to comply with sequence requirements.

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Upon reconsideration the species election requirement in paper #11 is vacated.
2. Claim 48 has been canceled and claims 47, 49-52 have been amended.
3. Claims 43-47, 49-59 are pending and under examination.

### ***Sequence Requirements***

4. It is noted that this application is in sequence compliance, however, the disc containing the substitute sequence listing submitted 10/28/02 was damaged as noted in the CRF Error report supplied with this Office Action. Although the CRF was damaged, the previously submitted CRF was used to search the SEQ ID Nos recited in the claims because those SEQ ID Nos were not altered as stated in the response filed 10/28/02 (see page 3). It is requested that a new CRF be supplied with the response to this Office Action as indicated on the Notice to Comply form enclosed with this Office Action.

### ***Claim Objections***

5. Claim 51 is objected to because of the following informalities: Claim 51 contains a typographical error in that SEQ ID NO: 115 is for a light chain not a heavy chain and SEQ ID NO: 116 is the sequence for a heavy chain. The claim will be interpreted to be a light chain of SEQ ID NO:115 and a heavy chain of SEQ ID NO:116. Appropriate correction is required.

***Specification***

6. The disclosure is objected to because of the following informalities:
- a. The first line of the specification should be updated to indicate 08/833,504 is no a provisional application 60/126,446.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 47, 49-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting VEGF-induced angiogenesis in a subject by administration of an antibody comprising a light chain with CDRL1 of SEQ ID NO:4, CDRL2 of SEQ ID NO:5, CDRL3 of SEQ ID NO:6 and a heavy chain with CDRH1 of SEQ ID NO:128 or 1, CDRH2 of SEQ ID NO:2, and CDRH3 of SEQ ID NO:129 or 3, does not reasonably provide enablement for a method of inhibiting VEGF-induced angiogenesis in a subject by administration of an antibody with the specified light chain sequence as recited in the claims and any heavy chain or an antibody with the CDRs specified in the claims and any light chain. The specification

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does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of inhibiting VEGF-induced angiogenesis with an antibody with specific CDRs of a light chain and any CDRs of a heavy chain or an antibody with specific CDRs from a heavy chain and any CDRs from any light chain. The specification teaches a method with specific antibodies with specific CDRs from a light chain and a heavy chain (see figures 1A-1B). the specification does not enable an antibody as broadly claimed in a method of inhibiting angiogenesis.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is

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characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function or can be used in the claimed method. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

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***Priority***

9. The instant application claims priority to provisional application 60/126,446, filed 4/7/97. Claims 43, recites the limitation of "a Kd value of no more than about  $1 \times 10^{-8}M$ " and claim 46 recites the limitation of "in an A673 in vivo tumor model". The limitations have support in the instant application, however, it appears that there is not support for these limitations in the 60/126,446 application. As such the priority date granted to claims 43-47, 49-59 is 8/6/97.

***Claim Rejections - 35 USC § 103***

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 43-47, 49-50, 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) and further in view of Adair et al (WO 91/09967, published 7/11/91) and Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and as evidenced from the specification.

The claims recite a method of inhibiting VEGF-induced angiogenesis in a subject by administration of an antibody wherein the subject has a tumor wherein the antibody binds no more than 10<sup>-9</sup>M, and 5mg/kg inhibits at least 50% of tumor growth in a A673 in vivo model, the antibody comprises CDRs recited in the claims, the antibody is a full length antibody, a IgG, and a Fab.

Ferrara et al teach an anti-VEGF antibody (see abstract). Ferrara et al also teach a humanized antibody (see page 8, lines 13-31) and the effect of the antibodies in tumor cell growth and angiogenesis (see page 23-24 and page 4). Ferrara et al also teach methods of inhibiting VEGF-induced angiogenesis in a subject and the subject can have cancer and the antibody was tested in a A673 model (see abstract and

Example 2) and the humanized antibody binds with 10<sup>-9</sup>M affinity (see page 8). Ferrara et al does not teach a specific method for humanization or obtaining the CDR sequence of the antibody. This deficiency is made up for in the teachings of Adair et al and Yelton et al.

Adair et al teach a method of antibody humanization by CDR grafting and framework modifications and methods of obtaining the amino acid sequences of antibodies from hybridomas and fragments of the antibody such as Fabs (see abstract and entire document).

Yelton et al teach an affinity maturation method comprising alterations in the CDRs of the heavy chain (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inhibiting VEGF-induced angiogenesis in a subject with cancer by administration of a humanized antibody of Ferrara humanized by the methods of Adair et al and Yelton et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the claimed method with a humanized anti-VEGF antibody because "most Mabs are of rodent origin, they are naturally antigenic in humans and thus can give rise to an undesirable immune response termed the HAMA" (see page 2). In addition, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to produce the claimed method because Ferrara et al teach the antibody can be humanized and the tumors from A4.6.1 treated animals were smaller than those tumors in mice treated with a control antibody

(see Figure 5). In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the claimed method because Yelton et al teach a method for affinity maturation of an antibody in order to "change the form, affinity, and potentially the specificity of Abs to optimize them for delivering a wide variety of therapeutic agents to tumor cells." (See page 2002 last paragraph)

Moreover, it would have been obvious to humanize the A4.6.1 antibody of Ferrara et al by the methods of Adair et al and Yelton et al because Ferrara et al teach human VEGF and in view of Adair and Yelton et al it would be obvious to humanize the antibody for therapy for inhibiting VEGF-induced angiogenesis.

As evidenced from the specification the A4.6.1 antibody of Ferrara et al has the CDRs as recited in claims 47, 49-50 (see Figure 1A and 1B of the specification).

It is the Examiner's position that the antibody produced by humanizing Ferrara et al's antibody with Adair et al's and Yelton et al's method would produce a humanized antibody that would have the binding and inhibition characteristics claimed in the claimed method. One of ordinary skill in the art would reasonably conclude that Ferrara et al's antibody humanized with Adair et al's and Yelton et al's method also possesses (1) the same binding affinity to the human VEGF, and (2) inhibits angiogenesis and tumor growth of at least about 50% in A673 in vivo tumor model, therefore, it appears that Ferrara et al's antibody humanized with Adair et al's and Yelton et al's method would produce a humanized antibody that is identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed humanized antibody with the humanized antibody of Ferrara et

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al's antibody humanized with Adair et al's and Yelton et al's method, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibody and the antibody of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

12. Claims 43-47, 49-50, 53-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara et al (WO 94/10202, published 5/11/94) and further in view of Adair et al (WO 91/09967, published 7/11/91) and Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and as evidenced from the specification as applied to claims 43-47, 49-50, 53-56 above, and further in view of Lopez et al (Invest Ophthalmol and Visual Science 37:855, 4/96).

Claims 43-47, 49-50 and 53-56 have been described supra. Claims 57-59 recite wherein the subject has age related macular degeneration and the antibody is administered at a dose of at least about 0.5 mg/kg.

Ferrara et al has been described supra. Ferrara et al also teach administration at 0.1 to 100 mg/kg (see page 15). Ferrara et al does not teach a humanized antibody by administration to a subject with age related macular degeneration. This deficiency is made up for in the teachings of Lopez et al.

Adair et al and Yelton et al have been described supra.

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Lopez et al teach VEGF may be important in the progression of ARMD (see page 865) and VEGF is a critical factor in CNVM development (see page 856).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inhibiting VEGF-induced angiogenesis in a subject with cancer by administration of a humanized antibody of Ferrara humanized by the methods of Adair et al and Yelton et al.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method of inhibiting VEGF-induced angiogenesis in a subject with AMD by administration of a humanized antibody of Ferrara humanized by the methods of Adair et al and Yelton et al in view of Lopez et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the claimed method because Ferrera et al teach the methods for inhibition of angiogenesis in a subject with many diseases and in view of Lopez which teaches VEGF is involved in angiogenesis in ARMD it would be obvious to inhibit ARMD with a humanized antibody to VEGF.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### ***Conclusion***

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13. No Claims are allowed. Claims 51 and 52 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

A handwritten signature in black ink, appearing to read 'L. Helms', is positioned to the right of the typed name 'Larry R. Helms Ph.D.'.

Application No. 09/723752

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☐ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☒ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other: \_\_\_\_\_

**Applicant Must Provide:**

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

For PatentIn software help, call (703) 308-6856

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